

Stereochemistry of α -Halogeno-sulphoxides. Part 5.¹ Absolute Stereochemistry of α -Chlorination of Benzyl *t*-Butyl Sulphoxide

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α -Halogenation of benzyl *t*-butyl sulphoxide (2) by electrophilic halogenating agents in pyridine affords a mixture of the diastereoisomeric α -halogenobenzyl *t*-butyl sulphoxides in the ratio 5 : 1. In the case of the (*R*)-sulphoxide (2), chlorination involves selective replacement of the *pro-R*-hydrogen atom and occurs both with inversion at sulphur and retention at carbon (major path) and with retention at both sulphur and carbon (minor path).

ELECTROPHILIC reactions of the α -lithio-derivatives of benzyl methyl (1) and benzyl *t*-butyl sulphoxide (2) with various reagents (D_2O , Me_2CO , MeI, and CO_2) have been studied recently.²⁻⁵ Lithiation of (*S*)-(1) † followed by quenching with D_2O or MeI afforded as major products (*S,S*) ‡ - α -deuteriobenzyl methyl sulphoxide (3a) and

(*R,S*)- α -methylbenzyl methyl sulphoxide (4a), respectively. The corresponding diastereoisomers (*R,S*)-(3b) and (*S,S*)-(4a) were formed in minor amounts, with the diastereoisomeric ratios (3a) : (3b) and (4a) : (4b) 15 : 1 in both cases.²⁻⁴

On the other hand, from (*R*)-(2) only (*R,R*)- α -deuterio-

² (a) R. Viau and T. Durst, *J. Amer. Chem. Soc.*, 1973, **95**, 1346; (b) T. Durst, R. Viau, and M. R. McClory, *ibid.*, 1971, **93**, 3066; (c) T. Durst and M. Molin, *Tetrahedron Letters*, 1975, 63.

³ K. Nishiata and M. Nishio, (a) *J.C.S. Perkin II*, 1972, 1730; (b) *Tetrahedron Letters*, 1972, 4839.

⁴ M. B. D'Amore and J. I. Brauman, *J.C.S. Chem. Comm.*, 1973, 398.

⁵ K. Nishiata and M. Nishio, *Tetrahedron Letters*, 1976, 1695.

† Ambiguity can arise from the fact that the sign of optical rotation of (*S*)-(1) is affected by the solvent; *e.g.* its sign is positive in ethanol, but negative in chloroform.

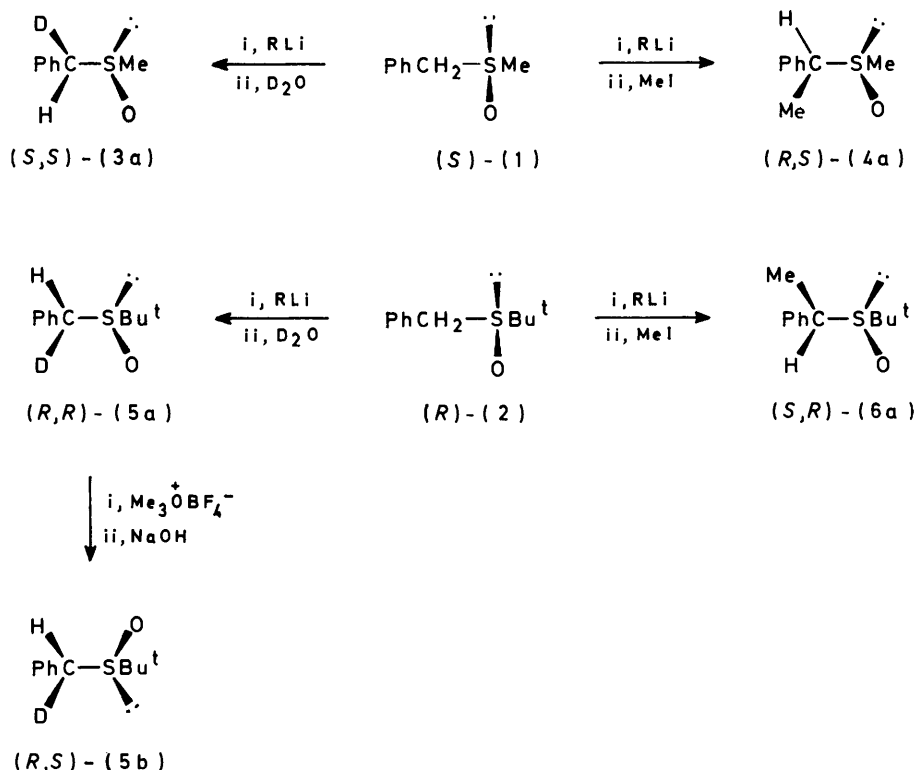
‡ In the present paper the absolute configuration cited first always refers to the asymmetric carbon atom.

¹ Part 4, M. Cinquini, S. Colonna, and F. Montanari, *J.C.S. Perkin I*, 1974, 1723.

benzyl t-butyl sulphoxide (5a) and the (*S,R*)- α -methylbenzyl t-butyl derivative (6a) were obtained.^{2,3} Two features are noteworthy: (a) the dependence of the stereochemical course of the reactions on the nature of the substrate and on the reagent; (b) the difference in stereoselectivity between reactions of compounds (1) and (2).

In a previous paper⁶ we have shown that α -halogenation of (*S*)-(1) with (dichloriodo)benzene or bromine in pyridine affords diastereoisomerically pure (*S,R*)- α -chloro- (7) or α -bromo- (8) benzyl methyl sulphoxide

The reaction has been shown to involve the *pro-R* hydrogen atom in (*R*)-(2) as follows. Chlorination and bromination of the racemic deuterio-derivative (*R,R/S,S*)-(5a) gives mixtures of the diastereoisomeric α -chloro-benzyl t-butyl sulphoxides (*R,R/S,S*)-(11) and (*R,S/S,R*)-(13) and of the diastereoisomeric α -bromobenzyl t-butyl sulphoxides (*R,R/S,S*)-(12) and (*R,S/S,R*)-(14), respectively. When the reactions were repeated with (*R,S/S,R*)-(5b), prepared from (*R,R/S,S*)-(5a) *via* inversion at the sulphinyl group, mixtures of the diastereoisomeric α -chloro- α -deuteriobenzyl t-butyl sulphoxides



SCHEME 1

together with (*R*)-chloro- (9) or -bromo- (10) methyl benzyl sulphoxide, as the reaction (1) \rightarrow (7) or (8) occurs with inversion at sulphur and retention at carbon and involves the *pro-S* hydrogen atom in (*S*)-(1).⁶ In view of the striking differences encountered between the electrophilic reactions of the methyl (1) and the t-butyl derivative (2), we have examined the α -halogenation of the latter.

Halogenation of benzyl t-butyl sulphoxide (2) with (dichloriodo)benzene or bromine in pyridine is less stereoselective than that of (1), and affords the diastereoisomeric α -halogenobenzyl t-butyl derivatives (11) and (13) or (12) and (14), respectively, in the ratio *ca.* 5 : 1.

Silver(I) nitrate, which has been shown¹ to influence the diastereoisomer ratio in the halogenation of thian S-oxides, has no effect on the diastereoisomeric composition of the product (see Experimental section).

⁶ M. Cinquini, S. Colonna, and F. Montanari, *J.C.S. Perkin I*, 1974, 1719.

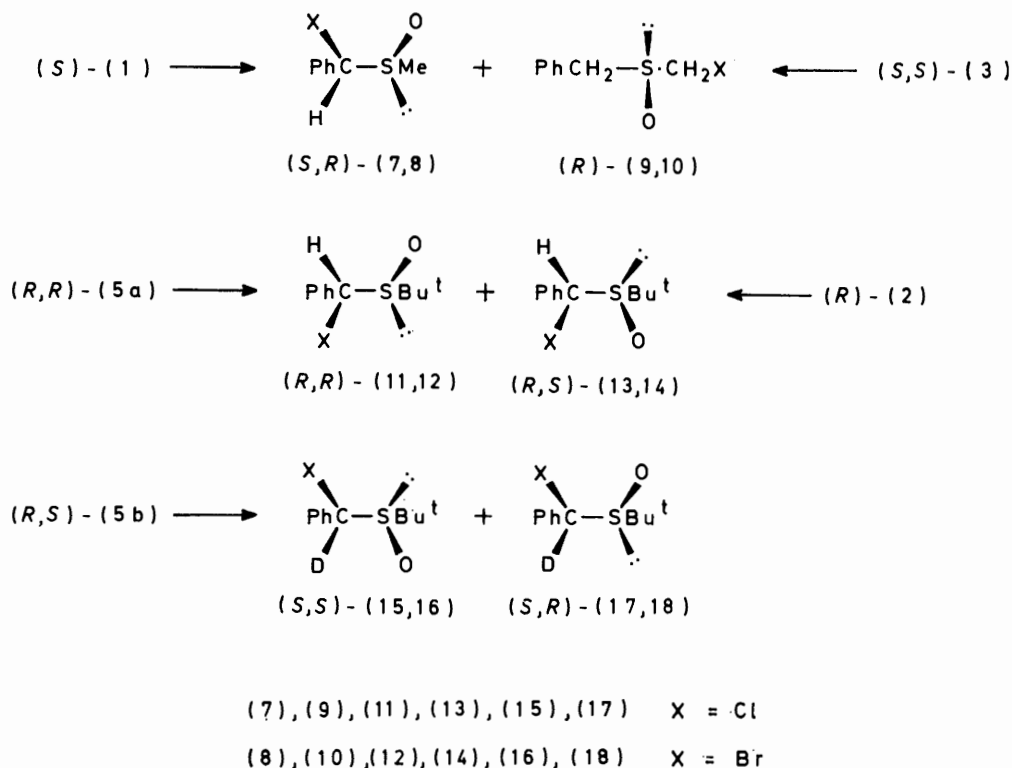
(*S,S/R,R*)-(15) and (*S,R/R,S*)-(17) and of the diastereoisomeric α -bromo- α -deuteriobenzyl t-butyl sulphoxides (*S,S/R,R*)-(16) and (*S,R/R,S*)-(18), respectively, were obtained (see Scheme 2).

In order to elucidate the stereochemical course of the reaction, optically active (+)-(*R*)-benzyl t-butyl sulphoxide (2), $[\alpha]_D^{25} +216^\circ$ (in CHCl_3), 82% optically pure,⁷ was chlorinated with (dichloriodo)benzene. (*R,R*)- α -chlorobenzyl t-butyl sulphoxide (11), $[\alpha]_D^{25} -29.1^\circ$ (in CHCl_3), m.p. 41–43°, and the diastereoisomeric (*R,S*)-(13), $[\alpha]_D^{25} +58.2^\circ$ (in CHCl_3), m.p. 76–78°, were obtained, in the ratio 85 : 15, and separated by column chromatography. When the reaction was repeated in the presence of silver(I) nitrate, (*R,R*)-(11), $[\alpha]_D^{25} -66.1^\circ$ (in CHCl_3), m.p. 57–58°, and (*R,S*)-(13), $[\alpha]_D^{25} +93.5^\circ$ (in CHCl_3), m.p. 84–86°, were obtained in the ratio 80 : 20. Therefore the presence of silver ions has

⁷ K. Mislow, M. M. Green, and M. Raban, *J. Amer. Chem. Soc.*, 1965, 87, 2761.

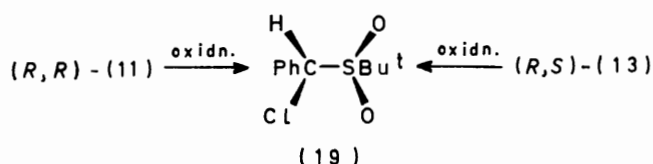
almost no effect on the diastereoisomer ratio, whereas it noticeably enhances the enantiomeric purity of both (11) and (13). Oxidation of the diastereoisomeric (–)-(11) and (+)-(13) gave the same (–)- α -chlorobenzyl t-butyl sulphone (19), thus showing that asymmetric

path) and also with retention both at sulphur and carbon (minor path). We emphasize that in this case also any stereomutation at carbon is accompanied by a concomitant stereomutation at sulphur, as always observed in the α -halogenation of sulphoxides.^{1,6,9,10}



SCHEME 2

induction at the α -carbon atom is involved in the chlorination and that (–)-(11) and (+)-(13) have the same configuration at carbon.



X-Ray analysis of the (–)-chloro-sulphone (19) by the anomalous scattering technique proved it to have the *R* absolute configuration.⁸ The *R* absolute configuration at carbon can thus be assigned to both chloro-sulphoxides (–)-(11) and (+)-(13). The relative configurations at sulphur and carbon in the sulphoxide (+)-(13) were also investigated by X-ray analysis⁸ and the *S* absolute configuration at sulphur assigned to (+)-(13). Therefore the prevailing diastereoisomer (–)-(11) as the *R,R* absolute configuration. This implies that the reaction of (R)-(2) [to give (R,R)-(11) and (R,S)-(13)] occurs with inversion at sulphur and retention at carbon (major

⁸ G. D. Andreotti, G. Bocelli, and P. Sgarabotto, personal communication.

⁹ P. Calzavara, M. Cinquini, S. Colonna, R. Fornasier, and F. Montanari, *J. Amer. Chem. Soc.*, 1973, **95**, 7431.

DISCUSSION

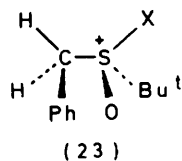
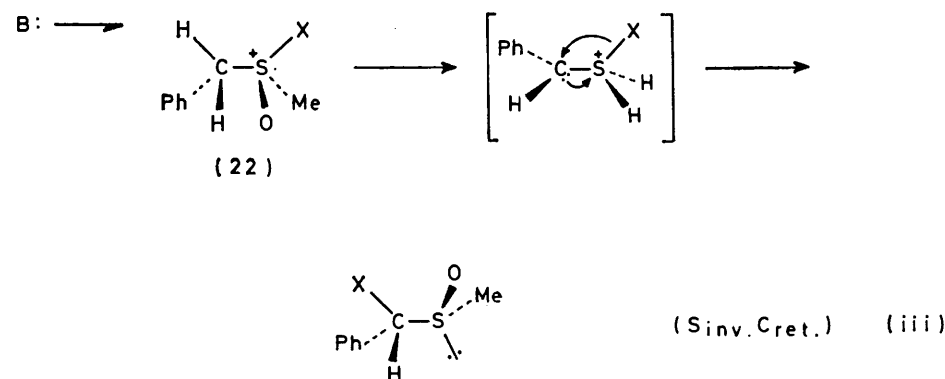
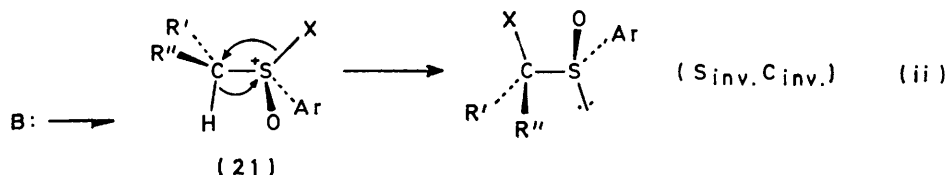
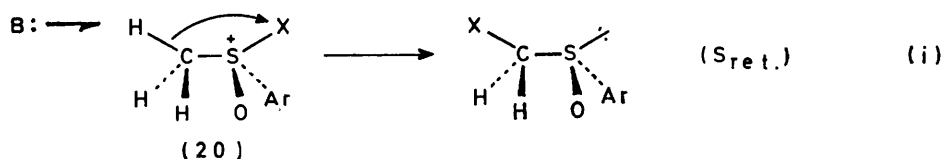
A comparison between the α -chlorination of benzyl methyl (1) and benzyl t-butyl sulphoxide (2) indicates that: (a) in both cases, with optically active sulphoxides (1) and (2), asymmetric induction from sulphur to the benzylic carbon occurs; (b) stereoelectronic factors determine in both cases the selective abstraction of one of the two benzylic hydrogen atoms, *i.e.* the *pro-S* atom in (S)-(1) and the *pro-R* atom in (R)-(2), which essentially occupy diastereotopic positions; (c) this behaviour tallies with that found in electrophilic reactions of methyl and t-butyl benzyl sulphoxides (see above);²⁻⁴ (d) α -halogenation of the t-butyl derivative (2) is less stereoselective than that of the methyl analogue (1); the experimental results indicate that the decrease in selectivity does not occur in the hydrogen abstraction from the chloro-oxosulphonium salt which has been shown¹⁰ to be the intermediate in the α -halogenation of sulphoxides.

In the α -halogenation of (2), two competitive processes of halogen transfer from sulphur to the α -carbon occur, processes which involve opposite stereochemical paths at sulphur but the same stereochemistry at carbon.

¹⁰ F. Montanari in 'Organic Sulphur Chemistry,' ed. C. J. M. Stirling, Butterworths, London, 1975, p. 181.

Different stereochemical courses have been previously found¹⁰ in the electrophilic halogenation of sulphoxides depending on the nature of the substrate and the reaction conditions. Scheme 3 shows the mechanisms proposed¹⁰ to account for the prevailing retention at sulphur, for

anion from sulphur to carbon, while an electron pair is transferred in the opposite direction. A situation similar to (ii) is represented in case (iii), where it is assumed that the carbanion is formed with inversion and not with retention. A tentative explanation of the



SCHEME 3

inversion at sulphur and carbon, and for inversion at sulphur and retention at carbon met with in the α -halogenation of methyl, branched alkyl aryl, and benzyl methyl sulphoxides, respectively. In every case any stereomutation at sulphur is accompanied by a concomitant stereomutation at carbon.^{*,10}

In case (i) it is assumed that attack by base on the *syn*-periplanar conformation (20) is concomitant with migration of a halogen cation from sulphur to carbon. Case (ii) involves attack by base on an *anti*-periplanar conformation and a concerted migration of halogen as

* This behaviour is formally analogous to that met with in diotropic reactions.¹¹

behaviour of *t*-butyl benzyl sulphoxide (2) is that attack of base occurs on a *syn*-periplanar conformation (23), and so the major path (S_{inv.}C_{ret.}) follows a mechanism similar to type (iii) in Scheme 3, previously proposed for benzyl methyl sulphoxide (1) and the minor one (S_{ret.}C_{ret.}) proceeds by a mechanism of type (i).

The choice between conformations (22) and (23) could be a result of differences in bulk between methyl and *t*-butyl groups, so that stereoelectronic interactions, in the order Ph-Bu^t > Ph-O > Ph-Me, are minimized in (22) and (23), respectively. This explanation has the

¹¹ M. T. Reets, (a) *Angew. Chem. Internat. Edn.*, 1972, **11**, 129; (b) *Tetrahedron*, 1973, **29**, 2189.

advantage that a common mechanism is invoked for all the substrates examined. Its limitations are the dependence of stereochemical results upon a conformational preference and the lack of a clear explanation for the retention or inversion of configuration of the carbanion involved.

The stereochemical results of the chlorination of cyclic sulphoxides, such as thian 1-oxides, have been explained in terms of an elimination-addition mechanism *via* 'inverted ylids'.^{11,12} Such a mechanism in our opinion hardly rationalises the high optical purity of the α -halogeno-derivatives obtained from optically active sulphoxides in open-chain systems and the dependence of the stereochemical course of the reaction on the nature of the substrate and on the reaction conditions.

EXPERIMENTAL

Light petroleum had b.p. 40–60 °C. ¹H N.m.r. spectra were recorded with a Varian A-60 spectrometer and optical rotations were measured with a Perkin-Elmer 141 polarimeter.

Benzyl t-butyl sulphoxide (2), obtained in 50% yield by oxidation of the corresponding sulphide with (dichloriodo)benzene in aqueous pyridine,¹³ had m.p. 74–75° (from light petroleum) (lit.,¹⁴ 71–72°).

(*R,S,R*)- α -Deuteriobenzyl t-butyl sulphoxide (5b), prepared in 62% yield from (5a) by reaction with trimethyl-oxonium tetrafluoroborate in methylene chloride followed by alkaline hydrolysis (NaOH) according to Johnson's procedure,¹⁵ had m.p. 73–74°.

(+)-(*R*)-Benzyl t-butyl sulphoxide, (*R*)-(2), obtained by the literature method,⁷ had m.p. 75–77°, $[\alpha]_D^{25} + 216^\circ$ (*c* 1 in CHCl₃) [lit.,⁷ $[\alpha]_D + 240^\circ$ (in CHCl₃), corresponding to an optical purity of 91%].

α -Halogeno-sulphoxides.— α -Halogenation of the sulphoxide (2) with (dichloriodo)benzene or bromine in pyridine in the presence or absence of silver(i) nitrate was carried out as previously described⁵ in pyridine-methylene chloride as solvent. Column chromatography (silica; diethyl ether-light petroleum, 1:4) separated the diastereoisomeric (*R,R,S,S*)- (11) and (*R,S,S,R*)- (13) α -chlorobenzyl t-butyl sulphoxides, m.p. 50–52 and 82–83°, respectively [Found: for (11): C, 57.4; H, 6.45. Found for (13): C, 57.25; H, 6.45. C₁₁H₁₅ClOS requires C, 57.25; H, 6.55%]. δ for (11) (CDCl₃) 1.25 (9 H, s, Bu^t), 5.55 (1 H, s), and 7.3–7.6 (5 H, m, aromatic); for (13) (CDCl₃) 1.4 (9 H, s, Bu^t), 5.43 (1 H, s),

* On this basis, in the case of (*R,R*)-(2), the intermediate derived from *trans*-elimination of DCl from the chloro-oxosulphonium salt would have the two bulkiest groups, Ph and Bu^t, *cis* to each other.

¹² (a) S. Bory, R. Lett, B. Moreau, and A. Marquet, *Compt. rend.*, 1973, **276**, 1323; (b) S. Iriuchijima, M. Ishibashi, and G. Tsuchihashi, *Bull. Chem. Soc. Japan*, 1973, **46**, 921; (c) S. Iriuchijima and G. Tsuchihashi, *ibid.*, p. 929; (d) J. Klein and H. Stollar, *J. Amer. Chem. Soc.*, 1973, **95**, 7437.

and 7.3–7.6 (5 H, m, aromatic). The diastereoisomeric (*R,R,S,S*)- (12) and (*R,S,S,R*)- (14) α -bromobenzyl t-butyl sulphoxides were obtained as an inseparable mixture, m.p. 74–80° (Found: C, 48.2; H, 5.6. C₁₁H₁₅BrOS requires C, 48.0; H, 5.5%), δ for (12) (CDCl₃) 1.18 (9 H, s, Bu^t), 5.7 (1 H, s), and 7.4–7.65 (5 H, m, aromatic); for (14) (CDCl₃) 1.26 (9 H, s, Bu^t), 5.7 (1 H, s), and 7.4–7.65 (5 H, m, aromatic). From the α -deuterio-sulphoxide (5a), the α -halogeno-sulphoxides (11)–(14) were obtained; from the diastereoisomeric α -deuterio-sulphoxide (5b) the deuterio-derivatives (15)–(18) were isolated. Their physical properties were identical with those of the isotopically normal derivatives. Yields and diastereoisomer ratios are in the Table.

Optically Active α -Chloro-sulphoxides.— α -Halogenation with (dichloriodo)benzene of (+)-(*R*)-benzyl t-butyl sulphoxide, $[\alpha]_D^{25} + 216^\circ$ (in CHCl₃), gave (*R,R*)- α -chlorobenzyl t-butyl sulphoxide (11), $[\alpha]_D^{25} - 29.1^\circ$ (in CHCl₃), m.p. 41–43°, and the diastereoisomeric (*R,S*)-(13), $[\alpha]_D^{25}$

Halogenation of benzyl t-butyl sulphoxides

Sulphoxide	Halogenating agent	Products	Yield (%)	Diast. ratio ^a
(2)	PhICl ₂	(11), (13)	45	85 : 15
(2)	PhICl ₂ , AgNO ₃	(11), (13)	30	80 : 20
(5a)	PhICl ₂	(11), (13)	30	85 : 15
(5b)	PhICl ₂	(15), (17)	28	82 : 18
(2)	Br ₂	(12), (14)	10	90 : 10
(2)	Br ₂ , AgNO ₃	(12), (14)	23	87 : 13
(5a)	Br ₂ , AgNO ₃	(12), (14)	10	83 : 17
(5b)	Br ₂ , AgNO ₃	(16), (18)	8	90 : 10

^a By ¹H n.m.r. spectroscopy.

+ 58.2° (in CHCl₃), m.p. 76–78°, in the ratio 85 : 15, which were separated by column chromatography under the conditions described above. When the reaction was repeated in the presence of silver(i) nitrate (2 mol. equiv.); (*R,R*)-(11), $[\alpha]_D^{25} - 66.1^\circ$ (in CHCl₃), m.p. 57–58°, and (*R,S*)-(13), $[\alpha]_D^{25} + 93.5^\circ$ (in CHCl₃), m.p. 84–86°, were obtained in the ratio 80 : 20.

(-)-(*R*)- α -Chlorobenzyl t-Butyl Sulphone (19).—The diastereoisomeric α -chloro-sulphoxides (*R,R*)-(11) ($[\alpha]_D^{25} - 66.1^\circ$) and (*R,S*)-(13), ($[\alpha]_D^{25} + 93.5^\circ$) (5 mmol) in dichloromethane (10 ml) were separately oxidized with a slight excess of *m*-chloroperbenzoic acid at 0 °C for 24 h. Work-up afforded the corresponding *sulphone* (*R*)-(19) which was purified by column chromatography (silica; ether-light petroleum, 1:4); m.p. 93–95°, $[\alpha]_D^{25} - 50.7^\circ$ (in CHCl₃) from (*R,R*)-(11); m.p. 94–95°, $[\alpha]_D^{25} - 49.6^\circ$ (in CHCl₃) from (*R,S*)-(13) (Found: C, 53.45; H, 6.1. C₁₁H₁₅ClO₂S requires C, 53.55; H, 6.15%).

[6/1896 Received, 11th October, 1976]

¹³ G. Barbieri, M. Cinquini, S. Colonna, and F. Montanari, *J. Chem. Soc. (C)*, 1968, 659.

¹⁴ A. Cerniani, G. Modena, and P. E. Todesco, *Gazzetta*, 1960 **90**, 3.

¹⁵ C. R. Johnson and D. McCants, *J. Amer. Chem. Soc.*, 1965, **87**, 5404.